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09/558,472	04/25/2000	Michael R. Bristow	MYOG:004DIV1	8819

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/558,472	BRISTOW ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 12/29/03, has been entered. Claim 23 has been amended.

Claim 23 is currently pending under examination.

Information Disclosure Statement

Applicants' IDS, filed 10/02/03, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claim 23 under 35 U.S.C. 112, first paragraph, is maintained for reasons of record.

The claim as amended is directed to a method of treating myocardial failure in a human comprising administering an effective amount of transgene encoding for α-MHC, wherein expression of α-MHC provides improvement in left ventricular ejection fraction.

Applicants submit that the Examiner is incorrect in arguing that there is insufficient evidence that increase in α-MHC transcripts seen in patients being successfully treated leads to patient benefit. Applicants argue that when the mRNA level increases, it is common sense that a commensurate increase in protein

levels will follow, and that although it is not always the case, but it is a rare occurrence when protein and message levels do not correlate and that the burden is thus upon the Examiner to explain why the demonstrated increase in message would not be viewed as predicative of therapeutic efficacy for α-MHC gene therapy. See p. 3, 2nd ¶ of the Response.

Applicants' arguments are not persuasive. The Examiner has provided sufficient evidence to show that the instant invention is not enabled. The claimed invention is directed to methods of treatment myocardial failure by administering a transgene encoding for α-MHC. The method is directed to gene therapy, the state of the art of which is unpredictable with particular regard to factors such as limited transfection efficiency, rates of DNA degradation, the *in vivo* consequences of altered gene function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See Eck and Wilson, cited in the Office action mailed 5/11/01. Thus, the Examiner's argument is not directed to Applicants' arguments which asserts that the Examiner has provided insufficient evidence that an increase in α-MHC transcripts would lead to patient benefit. The instant rejection is based upon the unpredictability associated with the gene therapy art for sufficient expression of a particular transgene, the sufficient expression of the resulting protein, and particular vectors,

and methods of delivery which would result in a therapeutic effect [*i.e.*, an improvement in left ventricular function], as required by the claims.

Applicants further argue that they supplemented evidentiary record with a recent publication and a declaration with regard to why an increase in message would be viewed as predicative in α-MHC gene therapy in App. No. 09/415,733. Particularly, that the relied-upon study examined MHC expression as a function of improved disease-state phenotype, and that a direct correlation between α- and β-MHC levels and a diseased heart state. See pp. 3-4 of the Response.

The Examiner presumes that Applicants are referring to the Gorczynski declaration, filed 9/17/01. This Declaration was not found to be persuasive because it refers to the endogenous levels of MHC [α-MHC and β-MHC] expression in diseased hearts undergoing heart failure. See #3, p. 2 of the Declaration. Further, the Declaration states that, "The study takes advantage of the fact that β-andrenergic blocking, such as metoprolo and carvedilol, effectively improve systolic function and reverse the dilated cardiomyopathy phenotype. Thus, monitoring gene expression levels as a correlate of improvement in the phenotype provides valuable evidence regarding a relationship between expression of various genes and the disease state itself." However, these statements do not provide a correlation with the present invention with regard to the gene delivery of a transgene encoding α-MHC by any route of delivery, any promoter and any vector/delivery system provide sufficient production of α-MHC to affect myocardial failure because they only refer to endogenous levels of gene expression.

Applicants further direct the Examiner to Jones *et al.* [Reference No. C21 of Applicants' IDS filed 10/2/03] for further evidence. Particularly, that the ablation of the α-MHC gene and the relationship between α-MHC protein and mRNA levels of α-MHC and LVEF, the measure of heart function which Applicants use as the standard for improvement in the instantly claimed invention. Applicants quote Jones as saying the mammalian left ventricular function can be severely compromised by a gene dosage effect involving α-MHC, which suggests that increasing levels of α-MHC would be beneficial to LVEF. See p. 4 of the Response.

Jones has been considered, but not found to be persuasive. Jones is directed to the generation of α-MHC knockout (+/- and -/-) mice. Jones fails to address any of the previously stated unpredictabilities associated with the gene therapy art. Although Jones show partial rescue of the +/- phenotype, this does not correlate to provide improvement in LVEF by introduction of an α-MHC transgene into a human suffering from myocardial failure. Jones does not teach introduction of a transgene encoding α-MHC to treat myocardial failure, or show that introduction of such a transgene would improve LVEF. Although Jones may show a relationship between α-MHC protein levels and LVEF, this fails to provide specific guidance to enable the instant invention, with regard to the particular delivery route, particular vector, and unpredictable factors associated with gene therapy, such as those listed in the preceding paragraphs, such that therapy of myocardial failure by improvement in LVEF would be achieved.

With regard to what increase in α-MHC levels would be need to increase LVEF to achieve therapy, Applicants point to the above-referenced study which used β-adrenergic blocking agents to improve the systolic function of subjects who exhibited cardiomyopathy and it was found that there was a direct correlation between improvement in LVEF and levels of α-MHC and β-MHC; specifically that LVEF improved following treatment with β-adrenergic blocking agents, mRNA levels of α-MHC and β-MHC increased. See pp. 4-5, bridging ¶ of the Response.

It is reiterated that the Examiner's rejection of the claimed invention is not directed to a correlation between endogenous levels α-MHC and LVEF following treatment of β-adrenergic blocking agents. The Examiner's rejection is based upon the lack of teaching or guidance provided by the instant specification, or the art, and for reasons stated in the preceding paragraphs, with regard to the delivery of a transgene encoding α-MHC, the expression of the transgene in sufficient levels such that therapy (*i.e.*, improvement in LVEF) would be achieved in a human suffering from myocardial failure. Applicants argue that they have provided sufficient evidence that one of skill in the art could predict, with a reasonable expectation of success, with *in vivo* levels of α-MHC would be considered therapeutic. See p. 5, 2nd ¶. This is not found to be persuasive. The monitoring of endogenous levels of α-MHC would fail to predict levels of α-MHC transgene that would be required to result in therapy because transgene expression in *in vivo* gene therapy is not predictable for reasons of record and those in the preceding paragraphs. Applicants have failed to provide sufficient guidance to overcome these art-recognized

unpredictabilities such that one of ordinary skill in the art would be able to carry out the claimed method without undue experimentation.

Applicants argue that the Examiner is requiring clinical data in stating that they have not provided guidance or evidence to show a correlation to therapeutic levels of expression of an α-MHC transgene expression in an *in vivo* setting in a subject suffering from myocardial failure. See pp. 5-6 of the Response.

This is not found to be persuasive. The claims are directed to methods of treatment, which would inherently require a therapeutic expression of a transgene in order to produce the desired result, *i.e.,* improvement in LVEF. Thus, the specification must provide sufficient guidance or teachings to enable the instant invention. The specification fails to provide a correlation between the administration of a transgene encoding α-MHC and a therapeutic result (improvement in LVEF) in a human suffering from myocardial failure. The instant specification fails to overcome the art-recognized unpredictabilities associated with the gene therapy for reasons of record. The Examiner does not recall requesting clinical data with regard to the instant invention, and Applicants are invited to point by page, paragraph and line number as to where this requirement is requested by the Examiner.

Applicants provide art with regard to the enablement of gene therapy. For example, Alexander, Chien, and other papers reporting cardiac transgene expression [Davidson, Pachucki, Shinmura, Lenhart, Lazarous, Wickenden]. Applicants particularly point to Fromes *et al.* who teach the delivery of a gene to the

myocardium by intraperitoneal injection. Applicants point to other references to show that potential of direct injection of genes into the myocardium. Applicants argue that the success seen by Fromes and Hajjar has been built upon by other researchers, Schroder shows that the addition of anti-CD4 monoclonal antibodies improved gene transfer into rat cardiac grafts, O'Donnell teach that sarcoplasmic reticulum could be expressed in cardiac myocytes, del Monte show the effective transfer and expression of SERC2 into a rat heart through adenoviral gene transfer, Li show an AAV vector could be used to transfer a reporter gene and a therapeutic gene into the heart of a hamster, and Yue teach the treatment of cardiovascular disease using an AAV vector to deliver a therapeutic gene to the heart of a diseased mouse, wherein they saw the improvement of cardiovascular function and improvement in the disease state. These references, Applicants argue, provide adequate evidence of the value and enablement of α-MHC therapy.

Applicants' references have been considered but are not found to be persuasive for reasons of record. Firstly, many of the references cited by Applicants are post-filing as of Applicants' effective filing date. MPEP §2164.05 (a) states that the specification must be enabling as of the filing date of the Application. The Examiner has provided evidence that the state of the art, at the time of filing, was unpredictable. Furthermore, the references cited by Applicants are directed to particular modes of delivery, particular transgenes, which provide a particular effect. The claims, as broadly written, encompass delivery of an α-MHC transgene by any mode of delivery to an individual suffering from myocardial failure. For

example, particular of the references cited by Applicant [for example, Fromes], show successful delivery of a gene to the myocardium by intraperitoneal injection. Fromes teaches the expression of a marker gene beta-galactosidase, by injection of a replication-deficient adenovirus into the pericardiac sac of adult Wistar rats. Fromes does not teach methods of treatment myocardial failure, as the Wistar rats do not exhibit myocardial failure and the expression of the beta-galactosidase does not provide therapy for these rats. Furthermore, the mere expression of a marker gene fails to provide any correlation of therapy for the instantly claimed invention, because the claimed invention requires the expression of the α-MHC transgene to be sufficient to improve LVEF. As stated in previous Office actions, the art cited by the Examiner clearly indicates the unpredictable status of gene therapy in a general sense, as well as it specifically pertains to cardiac gene therapy. Although specific vectors, promoter, genes, and routes of administration might be or may have been effective for the treatment of a specific disease, which provides a specific effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels of duration and expression of a particular gene of interest (in the instant case, α-MHC) which results in a therapeutic effect (in the instant case, improvement in LVEF). As such, evidence pertaining to a specific vector, gene, promoter, route of administration and therapeutic effect must be correlative to what is claimed, and in the instant invention, a correlation cannot be drawn for reasons of record and those presented in the preceding paragraphs.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving α-MHC gene therapy, the lack of direction or guidance provided by the specification to carry out α-MHC cardiac therapy, as broadly claimed, by any vector, promoter, target cell, route of administration, the absence of working examples for the demonstration or correlation to achieving therapeutic α-MHC gene expression *in vivo*, and the breadth of the claims directed to any vector, promoter, target cell, route of administration, and the unpredictable and undeveloped state of the art with respect to gene therapy, and particularly cardiac gene therapy, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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